FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
215164US0PCT	09/926554

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/03407	14 April 2000	18 May 1999

TITLE OF INVENTION

COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND

APPLICANT(S) FOR DO/EO/US

DI SALLE Enrico et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report/Request for Priority
PCT/IB/304
PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926554	PCT/EP00/03407	215164US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	23 - 20 =	3	x $18.00	**$54.00**	
Independent claims	5 - 3 =	2	x $84.00	**$168.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	

TOTAL OF ABOVE CALCULATIONS =	**$1,112.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	**$0.00**	
SUBTOTAL =	**$1,112.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	**$0.00**	
TOTAL NATIONAL FEE =	**$1,112.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	**$0.00**	
TOTAL FEES ENCLOSED =	**$1,112.00**	
	Amount to be: refunded	$
	charged	$

a. ☒ A check in the amount of **$1,112.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Nov. 19 2001
DATE

215164US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

ENRICO DI SALLE ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLN :
(Based on PCT/EP00/03407)

FILED: HEREWITH :

FOR: COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please delete Claims 1-23.

Please add the following new claims:

24. (New) A pharmaceutical composition for use in breast cancer therapy in humans, said composition comprising:

(a) an antineoplastic agent and a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, or combination thereof, and

(b) an aromatase inhibitor and a pharmaceutically acceptable carrier, pharmaceutically acceptable diluent, or combination thereof,

wherein said antineoplastic agent and said aromatase inhibitor are present in superadditive antitumor effective amounts,

and further wherein the aromatase inhibitor is not aminogluthetimide, when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl.

25. (New) The pharmaceutical composition according to Claim 24, wherein the antineoplastic agent is selected from the group consisting of an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite, and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from the group consisting of exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

26. (New) The pharmaceutical composition according to Claim 24, wherein the antineoplastic agent is selected from the group consisting of an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

27. (New) The pharmaceutical composition according to Claim 26, wherein the antineoplastic agent is selected from the group consisting of doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from the group consisting of mitoxantrone and losoxantrone; the podophillotoxine compound is selected from the group consisting of etoposide and teniposide; the taxane compound is selected from the group consisting of paclitaxel and docetaxel; the vinca alkaloid is selected from the group consisting of vinblastine and vinorelbine; the alkylating agent is selected from the group

consisting of cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from the group consisting of fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from the group consisting of topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

28. (New) The pharmaceutical composition according to claim 26, wherein said pharmaceutical composition comprises 1, 2 or 3 antineoplastic agents selected from the group consisting of epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from the group consisting of exemestane, formestane, anastrozole, letrozole and fadrozole.

29. (New) The pharmaceutical composition according to claim 25, wherein the antineoplastic agent is selected from the group consisting of an anthracycline and a taxane compound, and the steroidal aromatase inhibitor is exemestane.

30. (New) The pharmaceutical composition according to Claim 28, wherein the composition comprises one or two antineoplastic agents selected from the group consisting of epirubicin and docetaxel, and the steroidal aromatase inhibitor is exemestane.

31. (New) The pharmaceutical composition, according to Claim 24, wherein:

- an effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;

- an effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;

- an effective antineoplastic amount of mitoxantrone is from about 10 mg/m^2 to about 20 mg/m^2;

- an effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;

- an effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;

- an effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;

- an effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;

- an effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and an effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

32. (New) The pharmaceutical composition according to claim 31, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about

200 mg, the amount of fadrozole is from about 0.5 to about 10 mg, the amount of letrozole from about 0.5 to about 10 mg, and the amount of anastrozole is from about 0.5 to about 10 mg.

33. (New) The pharmaceutical composition according to claim 31, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and the amount of formestane is from about 250 to about 500 mg.

34. (New) A pharmaceutical product comprising an antineoplastic agent and an aromatase inhibitor, wherein said agent and said inhibitor are present in amounts effective to produce a superadditive antitumor effect, and wherein the aromatase inhibitor is not aminogluthetimide when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, and wherein said product is capable of separate, simultaneous or sequential administration in breast cancer therapy in humans.

35. (New) A method for treating breast cancer in humans, said method comprising administering an antineoplastic agent to a human in need thereof and administering an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, wherein the aromatase inhibitor is not aminogluthetimide when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl.

36. (New) A method for treating breast cancer in humans, said method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, wherein said agent and said inhibitor are administered in amounts effective to produce a superadditive antitumor erect, and the aromatase inhibitor is not aminogluthetimide when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl.

37. (New) The method according to claim 36, wherein the antineoplastic agent is selected from the group consisting of an antineoplastic topoisomerase II inhibitor, an

antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from the group consisting of exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

38. (New) The method according to claim 37, wherein the antineoplastic agent is selected from the group consisting of an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

39. (New) The method according to claim 38, wherein the anthracycline compound is selected from the group consisting of doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from the group consisting mitoxantrone and losoxantrone; the podophillotoxine compound is selected from the group consisting of etoposide and teniposide; the taxane compound is selected from the group consisting paclitaxel and docetaxel; the vinca alkaloid is selected from the group consisting of vinblastine and vinorelbine; the alkylating agent is selected from the group consisting of cyclophosphamide ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from the group consisting 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from the group consisting of topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

40. (New) The method according to claim 38, wherein 1, 2 or 3 antineoplastic agents is selected from the group consisting of epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors is selected from the group consisting of exemestane, formestane, anastrozole, letrozole and fadrozole, are administered.

41. (New) The method according to claim 37, wherein the antineoplastic agent is selected from the group consisting of an anthracycline compound and a taxane compound, and the steroidal aromatase inhibitor is exemestane.

42. (New) The method according to claim 41, wherein one or two antineoplastic agents is selected from the group consisting of epirubicin and docetaxel, and the steroidal aromatase inhibitor is exemestane, are administered.

43. (New) The method according to claim 39, wherein:

- an effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;

- an effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;

- an effective antineoplastic amount of mitoxantrone is from about 10 mg/m^2 to about 20 mg/m^2;

- an effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;

- an effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;

- an effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;

- an effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;

- an effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and an effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

44. (New) The method according to claim 42, wherein the one or two antineoplastic agents and the steroidal aromatase inhibitors are administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, the amount of fadrozole is from about 0.5 to about 10 mg, the amount of letrozole is from about 0.5 to about 10 mg, and the amount of anastrozole from about 0.5 to about 10 mg.

45. (New) The method according to claim 42, wherein the one or two antineoplastic agents and the steroidal aromatase inhibitors are administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and the amount of formestane is from about 250 to about 500 mg.

46. (New) A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, said method comprising administering to a human in need thereof a pharmaceutical composition comprising (a) an antineoplastic agent and (b) an

aromatase inhibitor, wherein said agent and said inhibitor is present in a quantity to produce a superadditive antitumor effect, and the aromatase inhibitor is not aminogluthetimide when the antineoplastic agent is a combination consisting of a cyclophosphamide, doxorubicin and 5-fluorouracyl.

47. (New) The method according to claim 40, wherein:

- an effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;

- an effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;

- an effective antineoplastic amount of mitoxantrone is from about 10 mg/m^2 to about 20 mg/m^2;

- an effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;

- an effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;

- an effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;

- an effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;

- an effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;

- an effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;

- an effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;

- an effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and an effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

REMARKS

Claims 24-47 are active in the present application. Claims 1-23 have been cancelled. Support for new Claims 24-47 can be found in the original claims. No new matter is believed to have been added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

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IN THE CLAIMS

Please delete Claims 1-23.

Please add new Claims 24-47.

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(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I–20152 Milan (IT).

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Published
With international search report.
With amended claims.

(54) Title: COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND

(57) Abstract

A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect: (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent.

Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound.

Field of the invention

The present invention relates to a method of treatment of human breast cancer and in particular to combination therapy involving administration of an aromatase (estrogen synthetase) inhibitor in combination with mono-or-polichemotherapy with cytotoxic agents.

Background of the invention

Since 1896 it has been demonstrated by Cecil Beatson that ovariectomy resulted in tumor regression in premenopausal breast cancer patients. Subsequently, estrogens were identified as the mediator of ovarian dependency. The biological effect of estrogens was found to be mediated by the stimulation of a nuclear estrogen receptor (ER), which belong to a family of hormone-activated transcription factors that can initiate or enhance the transcription of genes containing specific hormone response elements. Further, the sensitivity of breast cancer to estrogens has been found to increase in tumors positive for ER.

Over the last two decades, several approaches have been attempted to develop pharmacological agents able to reduce estrogen effect. Two pharmacological approaches are currently available:

1) the antiestrogens, which antagonize the effect of estrogens at the ER level;

2) the aromatase (estrogen synthetase) inhibitors, which inhibit the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively.

The prototype antiestrogen, tamoxifen, is now largely used in the adjuvant systemic therapy of localized breast cancer (i.e., systemic therapy given at the time of primary local treatment in the absence of demonstrated metastasis) and in the treatment of the advanced (metastatic) breast cancer. However, resistance to tamoxifen occurs, due to: 1) the intrinsic estrogenic effect of tamoxifen (i.e., partial estrogen agonism); 2) the formation of tamoxifen's estrogenic metabolites; 3) the stimulation by tamoxifen and

its metabolites of a mutated ER; 4) the growth of estrogen independent tumor cells. In addition, some concerns are now being considered in the use of tamoxifen in the early disease, due to the increased risk of endometrial cancer.

Therefore, new hormonal therapies without the negative effects of either tamoxifen or other similar compounds are under extensive evaluation.

One of such new antihormonal treatment modality of breast cancer is represented by the aromatase inhibitors. In the premenopausal women the ovarian aromatase is the main source of circulating estrogens. In the postmenopausal women adipose tissue is considered to be the main site for estrogen synthesis. In addition, aromatase activity has been shown in the breast tissue, including the tumor itself. Therefore, the very high levels of intratumoral estrogens in comparison to the circulating estrogens are due to the local estrogen synthesis through the aromatase enzyme.

Various steroidal and non-steroidal compounds have been described as aromatase inhibitors, including the steroidal derivatives exemestane and formestane, and the non-steroidal derivatives aminoglutethimide, vorozole, fadrozole, letrozole, anastrozole and YM511 (K.M. Susaki et al. J. Steroid. Biochem. Molec. Biol. 58, 189-194, 1996).

Many clinical trials have shown that these compounds represent an effective second-line treatment for metastatic breast cancer refractory to tamoxifen.

In addition, these compounds are being clinically evaluated in the adjuvant setting, either alone or combined with tamoxifen, and as first-line treatment of the metastatic disease.

The more complete estrogen blockade via aromatase inhibition is expected to result in greater tumor response than with tamoxifen, due to the weak or partial estrogen agonist effect of tamoxifen as above discussed.

Breast cancer was one of the first solid tumor to be treated with chemotherapy with cytotoxic agents, and one of the first tumors to be treated with polychemotherapy. Menopausal status and ER status play important role in therapy selection either in early or metastatic breast cancer. Chemotherapy is more commonly used in premenopausal women which are more likely to have ER-negative tumors. In the advanced disease, chemotherapy is recommended in the ER-negative tumors and after hormonotherapy failures in the ER-positive tumors. In several randomized trials, polychemotherapy has been established to the superior to monochemoterapy either in the adjuvant or

metastatic setting.

The cytotoxic compounds generally used in the polychemotherapy of breast cancer or under clinical evaluation belong to various classes including:

1) Topoisomerase II inhibitors, such as the antracyclines doxorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide.
2) Antimicrotubule agents, such as the taxanes paclitaxel and docetaxel, and the vinka alkaloids vinblastine and vinorelbine.
3) Alkylating agents, such as cyclophosphamide, ifosfamide and melphalan and the alkycycline derivative PNU-159548 (C. Geroni et al., Proc. Am. Assoc. Cancer Res 39, p223, 1998 (Abstr. #1517).
4) Antineoplastic antimetabolites, such as 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate.
5) Topoisomerase I inhibitors, such as topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804).

Despite intensive efforts directed at prevention and early diagnosis, breast cancer remains one of the leading causes of morbidity and mortality in women. Although early-stage disease is now frequently cured by surgical intervention and adjuvant hormonal and/or chemotherapy, the prognosis for women with advanced or with metastatic disease remains poor. In fact, a median survival of only 2-3 years has been consistently reported over the last 20 years, in spite of the introduction of novel agents. Therefore, in advanced breast cancer patients, palliation of symptoms remains one of the primary objectives of treatment, and maintaining a reasonable quality of life is of paramount importance. Hormonal therapy is often the treatment of choice in such patients. However, currently hormonal treatments of breast cancer cause, in patients not selected on the basis of their receptor status, only a maximal response rate of 30-35%. The median duration of response is 1 to 2 years and is influenced by the site of disease. If a patient's cancer responds to hormonal therapy but later progressed, the cancer may respond again to a second hormonal therapy, but the response rate decreases and the duration of response become shorter. Eventually, nearly all breast

cancers become refractory to hormonal manipulation and the patients are candidates for cytotoxic chemotherapy. Chemotherapy is more toxic than hormonal therapy, therefore is in general reserved for patients refractory to hormonal treatment or in patients with extensive visceral involvement, or if the tumor is growing rapidly. Combination chemotherapy is generally more effective than single agent treatment. However, only 15% of patients have a complete remission, the duration of the response is limited, all the tumors become resistant to chemotherapy and the patients die.

Therefore a major goal in breast cancer therapy is to develop new treatment modalities in order to increase tumor response and survival.

Accordingly, it would be desirable to have a drug combination modality having improved action than currently used treatment modalities. Ideally such combination should have increased efficacy, e.g. by providing both a better controlling of breast tumor growth and a longer duration of action, while resulting in less toxic side-effects, thus allowing administration of lower dosage levels of chemotherapeutic agent.

After an extensive study the present inventor has surprisingly found that the therapeutic effect of a chemotherapeutic cytotoxic (antineoplastic) agent is significantly improved and side-effects decreased by co-administering it with an aromatase inhibitor antitumor agent, i.e. a compound which inhibits the formation of estrogens by inhibiting the enzyme aromatase.

Description of the invention

In a first aspect, the present invention provides the use of an antineoplastic agent in the manufacture of a pharmaceutical composition for treatment of breast cancer, the treatment additionally comprising administration of at least one pharmaceutical composition comprising an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

The present invention also provides a product containing (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, as a combined preparation for simultaneous, separate or sequential use in breast cancer therapy in humans. Accordingly, the antineoplastic agent and the aromatase inhibitor may be present with a single of distinct container means.

The present invention also provides a composition of matter for use in breast cancer

therapy in humans, comprising (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, in amounts effective to produce a superadditive antitumor effect.

A further aspect of the present invention is a breast cancer therapy method for use in humans, in need thereof, the method comprising administering to said human (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

The invention also provides a method for lowering the side effects caused by breast cancer therapy with an antineoplastic agent in humans, in need thereof, the method comprising administering to said mammal a combination preparation of (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect.

Accordingly, said combination preparation can be used for lowering the side-effects caused by breast cancer antineoplastic therapy in mammals, including humans, while controlling the growth of neoplasm formation.

According to a preferred aspect of the present invention the superadditive antitumor effect results in an anti breast cancer therapy having increased effectiveness in controlling, i.e. slowing, interrupting, arresting, stopping or reversing, the neoplasm formation.

According to the present invention as "superadditive effect" is meant an effect in controlling the growth of the neoplasm, which is greater than the sum of the actions of the individual components. As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not necessarily indicate a total elimination of the neoplasm.

The term "antineoplastic agent" is meant to comprise both a single antineoplastic cytotoxic drug and "cocktails", i.e. mixtures of such drugs, according to the clinical practice.

The term "humans" is meant to comprise both female and male human beings.

In the combined preparations, pharmaceutical compositions and methods of treating, according to the present invention, the antineoplastic agent may comprise 1 to 4, preferably 1, 2 or 3, antineoplastic drugs, in particular a single antineoplastic drug.

The term "aromatase inhibitor" is meant to comprise both a single aromatase inhibitor agent and cocktails of such inhibitors.

In the combined preparations, pharmaceutical compositions and methods of treating, according to the present invention, the aromatase inhibitor preferably comprises 1 or a mixture of 2 aromatase inhibitor agents, in particular a single aromatase inhibitor agent.

The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can therefore be administered simultaneously, separately or sequentially to one and the same human being.

An antineoplastic agent, according to the invention, is preferably selected from the group comprising: an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor.

An antineoplastic topoisomerase II inhibitor is preferably:

a) an anthracycline compound e.g. doxorubicin (including liposomal formulations), epirubicin (including liposomal formulation), idarubicin and nemorubicin; and

b) an anthraquinone compound e.g. mitoxantrone and losoxantrone; and

c) a podophillotoxine compound e.g. etoposide and teniposide.

An antimicrotubule agent is preferably:

a) a taxane compound e.g. paclitaxel (including liposomal formulations) and docetaxel; and

b) a vinca alkaloid e.g. vinblastine and vinorelbine.

An alkylating agent is preferably cyclophosphamide, ifosfamide, melphalan and PNU 159548.

An antineoplastic antimetabolite agent is e.g. 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate.

An antineoplastic topoisomerase I inhibitor is e.g. topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

An antineoplastic agent is preferably epirubicin, doxorubicin, liposome-encapsulated doxorubicin, docetaxel, paclitaxel and liposome-encapsulated paclitaxel.

An aromatase inhibitor according to the present invention may be a steroidal

compound, in particular a steroidal compound selected from exemestane and formestane, or a non-steroidal compound selected from aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

Preferably an aromatase inhibitor is a compound selected from exemestane, formestane, anastrozole, fadrozole or letrozole, in particular exemestane.

Particularly preferred preparations, pharmaceutical compositions and methods of treating, according to the present invention, are those comprising a) 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and b) one or two, in particular one, steroidal aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

More preferably are those comprising a) one or two, in particular one, antineoplastic agent selected from epirubicin and docetaxel and b) exemestane.

Pharmacology

As stated above the present inventor has discovered that using a combination of an aromatase inhibitor and a cytotoxic agent it is possible to obtain a better control of the growth of breast tumor growth and a longer duration of tumor response.

The effect of the combination of the present invention is shown for instance by the following *in vivo* experiments which are intended to illustrate but not to limit the present invention.

Antitumor activity in dimethylbenzanthracene (DMBA)-induced mammary tumors in rats

Mammary tumors were induced by a single p.o. administration of 20 mg DMBA in 1 ml sesame oil. Tumors appeared starting about 40 days after DMBA administration. Rats were selected and placed sequentially into experimental group when at least 1 tumor of 1 cm of diameter was found. The two perpendicular tumor axes were measured with calipers once a week during the experiment. Tumor weight was calculated according to the formula $d^2xD/2$ where d is the minimal and D the maximal diameter.

Tumor growth of control and treated groups were expressed as ratio of initial tumor weight, measured the first day of treatment. At the end of the treatment period (week 4)

tumor response to the drug was designed as CR (complete remission, disappearance of the tumor), PR (partial remission, >50% reduction in tumor weight); NC (no change, ≤50% increase or decrease) or P (progression, >50% increase). In addition, the appearance of new tumors during the 4-week treatment regimen was evaluated.

Exemestane, dissolved in benzylic alcohol (3% of final volume) and diluted in sesame oil, was administered s.c., 6 days a week for 4 weeks. Epirubicin, dissolved in sterile 0.9% NaCl solution, was administered i.v., once a week for 4 weeks. Docetaxel, dissolved in 13% ethanol and diluted in 5% glucose solution, was administered i.v., once a week for 4 weeks.

Table 1. Effect of 4-week treatment with exemestane alone or combined with epirubicin on DMBA-induced mammary tumors in rats

Exemestane mg/kg/day s.c.	Epirubicin mg/kg/wk i.v.	No. of rats	No. of tumors	Tumor response (%)					No. of new tumors /rat	Body weight gain (g/4wks)
				CR	PR	CR+PR	NC	P		
Control		14	27	0	7	7	26	67	2.1	10
-	1	13	28	0	7	7	36	57	2.1	8
-	3	14	26	12	15	27	27	46	0.5	3
20	-	12	25	20	24	44	20	36	0.6	45
20	1	12	24	42	33	75	17	8	0.7	41
20	3	12	29	48	41	90	10	0	0.0	21

Results in Table 1 indicate that epirubicin was not effective (at 1 mg/kg/day, 7% CR+PR) or less effective (at 3 mg/kg/wk; 27% CR+PR) than exemestane (44% CR+PR) in inducing tumor regressions. When the two drugs were given in combination, a very interesting superadditive antitumor effect was observed in the combination of exemestane either with the low (75% CR+PR) or the high epirubicin dose (90% CR+PR). The appearance of new tumors was reduced by single treatment with epirubicin 3 mg/kg/wk and exemestane (alone or combined with epirubicin 1 mg/kg/wk). Again, very interestingly the combination of exemestane with epirubicin 3 mg/kg/wk totally prevented the appearance of new tumors during the 4-week of treatment period (2.1 tumors per rat in the control group, versus 0 tumor per rat in the group treated with the combination). Body weight gain indicated that epirubicin, at the tested doses, had a slight inhibitory effect while exemestane showed an anabolizing effect either alone or given in combination.

Figure 1 in particular shows the effect of exemestane and epirubicin given alone or in combination on the growth of DMBA-induced tumors in rats, in which:

—✱— Control

—○— EPI 1 mg/kg/wk

—●— EPI 3 mg/kg/wk

—▲— EXE 20 mg/kg/day

- ◻ - EXE + EPI 1

- ■ - EXE + EPI 3

Figure1 illustrates tumor growth (expressed as ratio of initial tumor weight) during the 4-week treatment period of control and treated groups. The single treatment with exemestane or epirubicin 3 mg/kg/wk caused a reduction of tumor growth, however a higher antitumor effect was observed when the two drugs were combined. Interestingly combined treatments resulted in a longer duration of tumor response: in fact 4 weeks after the end of the treatment (week 8) tumor regrowth was completed in the groups treated with single agents while in the group treated with the combination of exemestane and epirubicin 3 mg/kg/wk tumor weight was still inhibited.

Table 2. Effect of 4-week treatment with exemestane alone or combined with docetaxel on DMBA-induced mammary tumors in rats

Exemestane mg/kg/day s.c.	Docetaxel mg/kg/wk i.v.	No. of rats	No. of Tumors	Tumor response (%) CR	PR	CR+PR	NC	P	No. of new tumor /rat	Body weight gain (g/4wks)
Control		14	27	0	7	7	26	67	2.1	10
-	1.5	13	29	17	24	41	28	31	0.4	0
20	-	12	25	20	24	44	20	36	0.6	45
20	1.5	12	24	75	17	92	4	4	0.0	28

Table 2 shows the results obtained combining exemestane and docetaxel. Docetaxel at 1.5 mg/kg/wk was effective inducing 41% tumor response (CR+PR), an effect similar to that observed after exemestane treatment (44% tumor response). When the two drugs were combined a super additive effect was observed, and almost all tumor regressed (92%). Also the appearance of new tumors was completely suppressed (0 tumor per rat) only with the combination.

It is of note that no obvious increased general toxicity was ever observed with the

combinations, as evaluated for instance in terms of body weight loss.

Figure 2 shows the time-course effect of 4-week treatment with exemestane alone or combined with docetaxel on DMBA-induced mammary tumors in rats, in which:

—✱— Control
—○— DOCE 1.5 mg/kg/wk
—●— EXE 20 mg/kg/day
—▲- EXE + DOCE 1.5

As illustrated in Figure 2, the effect of the combination of exemestane and docetaxel was higher than that of single agent and tumor remissions lasted for longer time.

These results support the utilization of an antineoplastic agent in therapy in combination with an aromatase inhibitor antitumor agent.

As used herein, the term "effective antineoplastic amount" refers to an amount which is effective, upon single or multiple dose administration to the patient, in controlling the growth of the neoplasm or in prolonging the survivability of the patient beyond that expected in the absence of such treatment. As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not necessarily indicates a total elimination of the neoplasm.

An effective amount of an aromatase inhibitor antitumor agent may vary from about 0.5 to about 500 mg pro dose 1-2 times a day. Exemestane, for example, may be administered orally in a dosage range varying from about 5 to about 200 mg, and particularly, from about 10 to about 25 mg, or parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

Fadrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

Letrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2.5 mg.

Formestane, for example, may be administered parenterally in a dosage range varying from about 250 to about 500 mg, and particularly, from about 250 to about 300 mg.

Anastrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

The effective antineoplastic amounts of the various antineoplastic agents are well known and appreciated in the art.

For example, an effective antineoplastic amount of vinblastine may vary from about 3 mg/m^2 to about 10 mg/m^2.

An effective antineoplastic amount of doxorubicin may vary from about 20 mg/m^2 to about 100 mg/m^2.

An effective antineoplastic amount of epirubicin may vary from about 20 mg/m^2 to about 200 mg/m^2.

An effective antineoplastic amount of idarubicin may vary from about 1 mg/m^2 to about 50 mg/m^2.

An effective antineoplastic amount of mitoxantrone may vary from about 10mg/m^2 to about 20 mg/m^2.

An effective antineoplastic amount of paclitaxel may vary from about 100 mg/m^2 to about 300 mg/m^2.

An effective antineoplastic amount of docetaxel may vary from about 50 mg/m^2 to about 100 mg/m^2.

An effective antineoplastic amount of vinorelbine may vary from about 15 mg/m^2 to about 30 mg/m^2.

An effective antineoplastic amount of cyclophosphamide may vary from about 100 mg/m^2 to about 1500 mg/m^2.

An effective antineoplastic amount of melphalan may vary from about 1 mg/m^2 to about 10 mg/m^2.

An effective antineoplastic amount of 5-fluorouracil may vary from about 100 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of capecitabine may vary from about 10 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of methotrexate may vary from about 10 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of topotecan may vary from about 1 mg/m^2 to about 5 mg/m^2.

An effective antineoplastic amount of irinotecan may vary from about 50 mg/m^2 to about 350 mg/m^2.

In effecting treatment of a patient afflicted with a disease state described above an aromatase inhibitor can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, it can be administered orally, subcutaneously, intraperitoneally, intramuscularly, intravenously, transdermally, and the like. Oral or intramuscular administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular circumstances, including the disease state to be treated, the stage of the disease, the form of administration of the selected cytotoxic agent and the manner of co-administration selected.

For example, GB-2,177,700 discloses the preparation of pharmaceutical compositions comprising exemestane and a suitable carrier or excipient.

The selected antineoplastic agent can be administered by the appropriate route and dosing schedule as is well known and accepted for the particular agent. For example, epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinblastine can be administered intravenously. Idarubicin and cyclophosphamide can also be given orally.

Claims

1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent.

2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

3. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin,

paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

6. A composition according to claim 5, wherein the composition comprises one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor is exemestane.

7. A composition, according to anyone of the preceding claims, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to

about 1000 mg/m^2;

- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

8. A composition according to claim 7, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

9. A composition according to claim 7, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.

10. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans.

11. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

12. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

13. A method, according to claim 12, wherein the antineoplastic agent is

selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

14. A method according to claim 13, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

15. A method according to claim 14, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

16. A method according to claim 14, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

17. A method according to claim 15, wherein one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor exemestane are administered.

18. A method according to claim 15 or 16, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

19. A method according to claim 18, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

20. A method according to claim 18, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.

21. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect.

Claims

1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite, and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

3. A composition according to claim 2. wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

6. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline and a taxane compound and the steroidal aromatase inhibitor is exemestane.

7. A composition according to claim 5, wherein the composition comprises one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor is exemestane.

8. A composition, according to anyone of the preceding claims, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;

- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1. mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

9. A composition according to claim 8, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

10. A composition according to claim 8, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.

11. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

12. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

13. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

14. A method, according to claim 13, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

15. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

16. A method according to claim 15, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-

fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

17. A method according to claim 15, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

18. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound and a taxane compound and the steroidal aromatase inhibitor is exemestane.

19. A method according to claim 18, wherein one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor exemestane are administered.

20. A method according to claim 16 or 17, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10 mg/m^2 to 10 about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;

- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 30 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

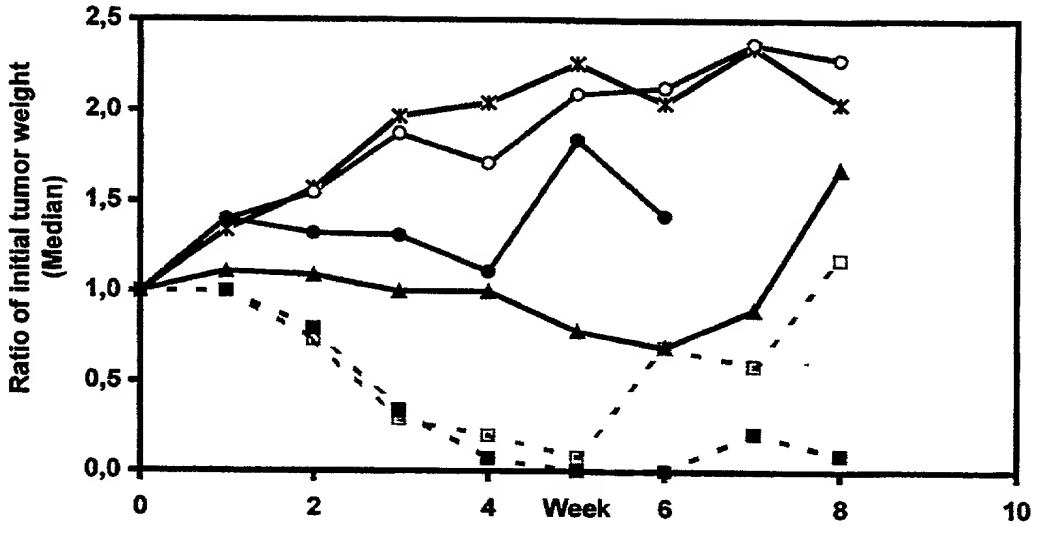
21. A method according to claim 19, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

22. A method according to claim 19, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.

23. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of

cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

Fig. 1


Ratio of initial tumor weight (Median)
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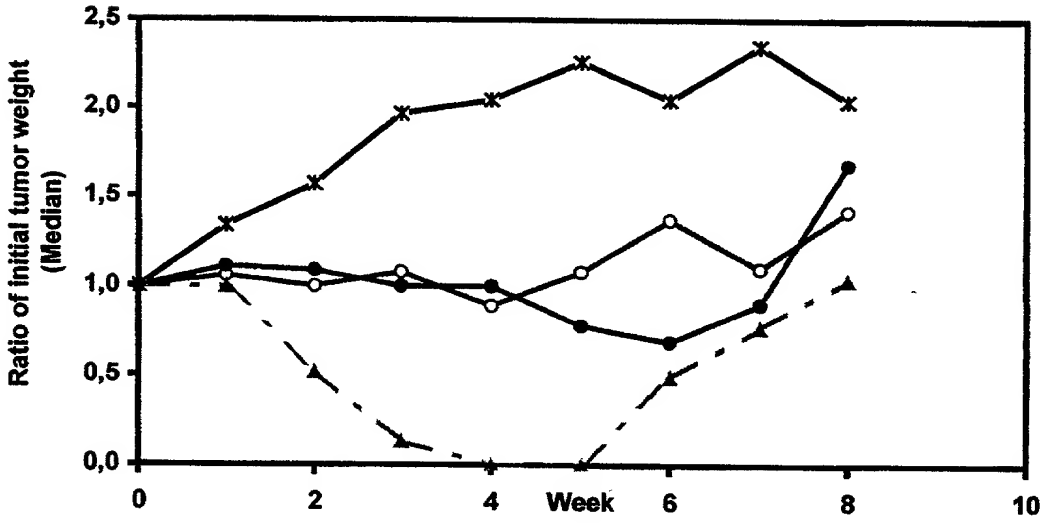
1,0
0,5
0,0
0
2
4
Week
6
8
10

Fig. 2


Ratio of initial tumor weight (Median)
2,5
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0,0
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2
4
Week
6
8
10

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number PCT/EP00/03407

on April 14, 2000,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
9911582.6	Great Britain	18 May 1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Steven B. Kelber, Reg. No. 30,073; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Martin M. Zoltick, Reg. No. 35,745; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Marc R. Labgold, Reg. No. 34,651; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Catherine B. Richardson, Reg. No. 39,007; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Sharon E. Crane, Reg. No. 36,113; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; and Paul E. Rauch, Reg. No. 38,591; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Post Office Address:

Date